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(54) **MANUFACTURING METHOD FOR MEDICAL EQUIPMENT FOR REDUCING PLATELET ADHESION OF A SURFACE IN CONTACT WITH BLOOD**

(57) A manufacturing method for medical equipment wherein an electron beam is irradiated on a titanium or titanium alloy substrate surface that has at least been machined, and the platelet adhesion of a surface which is in contact with blood is reduced; and a manufacturing method for medical equipment that uses a specific pre-processing method and an electron beam irradiation method to reduce the platelet adhesion of a surface which is in contact with blood, and which suppresses the formation of minute depressions (craters) in the surface, which can occur due to the irradiation of an electron beam.

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Description

TECHNICAL FIELD

[0001] The present invention relates to a method of manufacturing a medical device and particularly to a method of manufacturing a medical device whereby a surface brought into contact with blood has reduced platelet adhesion.

BACKGROUND ART

[0002] Among titanium or titanium alloy base materials are pure titanium (e.g. JIS Class 1 and 2) and high-strength titanium alloys exemplified by α-β alloys, 6-4 alloys (e.g. JIS Class 60), β alloys, and 15-3-3-3 alloys. Among titanium or titanium alloy base materials used for medical metallic devices are 6-4 alloys and ELI (Extra Low Interstitial Elements) materials that are 6-4 alloys containing oxygen, nitrogen, hydrogen, and iron in particularly reduced amounts. The 6-4 alloys and ELI materials possess a high strength and consistently maintain their high strength even at a high temperature but are difficult to machine, easily wear, and are liable to develop seizure or galling.

[0003] A medical device made of a titanium or titanium alloy base material is manufactured by cutting or otherwise machining a block material, which is produced by, for example, rolling, into a given shape.

Cutting is implemented using an end mill. The surfaces of a medical device need to be so made that they inhibit adhesion of germs thereto and, when in contact with fluent blood, inhibit adhesion of platelets thereto and, hence, formation of blood clots. Cutting a titanium or titanium alloy base material surface with, for example, an end mill size-reduces crystal grains in the surface and leaves traces of cutting, thereby posing great problems in obtaining a surface inhibiting adhesion of germs thereto as required of medical devices.

In order to avoid the above problems, the machining is followed by, for example, buffing, chemical etching, or blast polishing.

[0004] However, these processes in turn present their problems: buffing is not applicable to a base material having a relatively complicated configuration; chemical etching exposes crystal grains of a base material; in blast polishing, pieces of a blasting material drive into a base material and remain in the base material surface. Polishing requires extended labor.

[0005] Heretofore, there is no known method of manufacturing a medical device using an electron beam irradiation process to reduce platelet adhesion of surfaces.

[0006] As described in Patent Literature 1 and non-patent Literature 1, there is known in the art a method whereby a metallic base material of pure titanium, a metal used in dentistry, is subjected to electron beam irradiation for improved surface flatness, enhanced glossiness, and increased corrosion resistance.

However, when a material other than pure titanium, chiefly a 6-4 titanium material or the like is subjected to electron beam irradiation for improved surface flatness, enhanced glossiness, and increased corrosion resistance in the same manner as used for pure titanium, impurities contained in the titanium material may develop small pits (hereinafter referred to as craters) in the outermost surface of the material as the outermost surface is caused to boil and vaporize by the electron beam irradiation, resulting in defects in the surface.

CITATION LIST

PATENT LITERATURE

[0007] Patent Literature 1: JP 2003-111778 A NON-PATENT LITERATURE

[0008] Non-Patent Literature 1: "Development of Dental Metal Surface Polishing Method using Electron Beam," PhD dissertation by Junko TOKUNAGA, Graduate School of Dentistry, Osaka University, March 2008.

SUMMARY OF INVENTION

TECHNICAL PROBLEMS

[0009] An object of the present invention is to provide a method of manufacturing a medical device having a surface inhibiting adhesion of germs thereto or a surface coming into contact with blood with reduced platelet adhesion.

SOLUTION TO PROBLEMS

[0010] The above object is achieved by the present invention described below.

(1) A method of manufacturing a medical device comprising subjecting a titanium or titanium alloy base material

surface having undergone at least a cutting process to electron beam irradiation to reduce platelet adhesion of a surface that comes into contact with blood.

(2) The method of manufacturing a medical device according to (1), wherein the electron beam irradiation is implemented after the surface is heat-treated.

(3) The method of manufacturing a medical device according to (1) or (2), wherein the electron beam irradiation comprises a first electron beam irradiation implemented with a first voltage and a second electron beam irradiation implemented with a second voltage that is higher than the first voltage.

(4) The method of manufacturing a medical device according to any one of (1) to (3), wherein the electron beam irradiation is implemented first by reverse-polarity electron beam irradiation using a pure titanium metal as an anode, followed by straight-polarity electron beam irradiation.

ADVANTAGEOUS EFFECTS OF INVENTION

[0011] The medical device obtained by the manufacturing method of the invention has a surface, which comes into contact with blood, with reduced platelet adhesion.
A medical device obtained by another manufacturing method of the invention has a surface, which comes into contact with blood, with reduced platelet adhesion and which surface inhibits formation of small pits (so-called craters) in the surface caused by electron beam irradiation.

BRIEF DESCRIPTION OF DRAWINGS

[0012]

[FIG. 1] FIG. 1 illustrates a metallic surface obtained as a comparative material in Example 1. FIG. 1(A) is a metallographic micrograph showing the surface of the comparative material obtained in Example 1 (20x magnification). FIG. 1(B) is a laser micrograph showing the surface of the comparative material obtained in Example 1. FIG. 1(C) is a diagram showing a measurement result of the surface roughness of the surface of the comparative material obtained in Example 1.

[FIG. 2] FIG. 2(A) is a photograph showing an image acquired by a TEM (transmission electron microscope) and representing a cross section of the comparative material obtained in Example 1. FIG. 2(B) is a photograph showing an image acquired by a TEM and representing a cross section of a base material irradiated by SOLO system.

[FIG. 3] FIG. 3 is a schematic diagram for explaining a large-area electron beam irradiator.

[FIG. 4] FIG. 4(A) is an exploded perspective view of a flow chamber. FIG. 4(B) is a top plan view of a flow chamber.

[FIG. 5] FIG. 5(A) is a micrograph showing platelets adherent to a specimen 1A. FIG. 5(B) is a photograph acquired under the same conditions for comparison to show a metallic surface that is out of contact with blood flow.

[FIG. 6] FIG. 6(A) is a micrograph showing platelets adherent to a specimen 21A. FIG. 6(B) is a photograph acquired under the same conditions for comparison to show a metallic surface that is out of contact with blood flow.

[FIG. 7] FIG. 7 is a schematic diagram illustrating shape change of a platelet as it is activated.

[FIG. 8] FIG. 8 shows a crater as observed with an atomic force microscope.

[FIG. 9] FIG. 9 is a photograph showing craters in a surface as observed with a metallograph (20x magnification).

[FIG. 10] FIG. 10 is a schematic diagram for explaining a SOLO system.

[FIG. 11] FIG. 11 (A) is a photograph acquired by a laser microscope and showing a result obtained by irradiation with SOLO system and subsequent electron beam irradiation in Example 2. FIG. 11(B) is a diagram showing a measurement result of the surface roughness of the surface shown in FIG. 11 (A).

[FIG. 12] FIG. 12 is a metallographic micrograph (20x magnification) showing a surface obtained by irradiation with SOLO system and subsequent electron beam irradiation in Example 2.

[FIG. 13] FIG. 13 is a surface micrograph representing the texture of a metal resulting from a process implemented in Example 3.

[FIG. 14] FIG. 14(A) is a surface micrograph acquired by a metallograph (20x magnification) and showing a surface obtained in a first stage in Example 4. FIG. 14(B) is a surface micrograph acquired by a metallograph (20x magnification) and showing a surface obtained in a second stage in Example 4.

[FIG. 15] FIG. 15 is a schema of an electron beam irradiator with a reverse polarity.

[FIG. 16] FIG. 16 is a surface micrograph acquired by a metallograph (20x magnification) representing the surface of a base material subjected to 2-stage electron beam irradiation in Example 5.

[FIG. 17] FIG. 17 illustrates a result of an abrasion-resistance test applied to a surface obtained in Example 3 and coated with DLC. FIG. 17(A) illustrates Rockwell indentations; FIG. 17(B) illustrates abrasion marks.

[FIG. 18] FIG. 18 illustrates a result of an abrasion-resistance test applied to a surface obtained in Example 4 and coated with DLC. FIG. 18(A) illustrates a Rockwell indentation; FIG. 18(B) illustrates abrasion marks.

[FIG. 19] FIG. 19 illustrates a result of an abrasion-resistance test applied to a surface obtained in Example 5 and coated with DLC. FIG. 19(A) illustrates a Rockwell indentation; FIG. 19(B) illustrates abrasion marks.
[FIG. 20 FIG. 20 is a longitudinal cross-section of a centrifugal blood pump device described in JP 2005-270345 A.
[FIG. 21] FIG. 21 is a transverse cross-section of the centrifugal blood pump device described in JP 2005-270345 A.
[FIG. 22] FIG. 22 is a cross section showing the centrifugal blood pump device of FIG. 21 with the impeller removed.

DESCRIPTION OF EMBODIMENTS

[0013] The method of manufacturing a medical device of the invention is described in detail below.

1. <Titanium or Titanium Alloy Base Material>

[0014] Titanium or titanium alloy base materials used for medical devices include pure titanium classified as JIS Class 1 and JIS Class 2 and Ti-6Al-4V(referred to below as 6-4 alloys), 6-4 alloy-based ELI materials (JIS Class 61), Ti - 6Al - 2Nb - 1Ta, Ti - 15Zr - 4Nb - 4Ta, Ti - 6Al - 7Nb, Ti - 3Al - 2.5V, Ti - 13Nb - 3Zr, Ti - 15Mo - 5Zr - 3Al, Ti-12Mo - 6Zr - 2Fe, and Ti - 15Mo.

2. <Machining>

[0015] A titanium or titanium alloy base material is made into a block material through, for example, a rolling process and then machined into a shape as used in a medical device. Machining may be implemented by a method as required for an individual medical device and is not particularly specified. In the manufacturing method of the invention, machining is implemented at least by cutting using mostly an end mill.
FIG. 1(A), FIG. 1(B), and FIG. 1(C) show results of an end-milled surface serving as a comparative material in Example 1 described later. When the titanium or titanium alloy base material is not pure titanium, traces of cutting are observed as illustrated in FIG. 1. FIG. 2(A) shows an image acquired by a transmission electron microscope (TEM) and representing a cross section of an end-milled base material. Size reduction of crystal grains is also observed.

3. <Electron Beam Irradiation>

[0016] FIG. 3 illustrates a schematic assembly of an electron beam irradiator used in the invention. FIG. 3 illustrates an electron beam irradiator using explosive electron emission (EEE) method.
A sample 9 is placed in a vacuum chamber 1 in which the pressure has been reduced to a vacuum by a vacuum pump 2 and an auxiliary vacuum pump 3, and electrons emitted from a cathode 7 hit anode plasma 8 generated by an anode 6 to further generate electrons (Penning effect). Numeral 5 denotes a solenoid; numeral 4 indicates an argon gas container.
Electron beam irradiation is implemented preferably under the following conditions: applied cathode voltage Vc = 10 kV to 30 kV; solenoid voltage Vs = 0.1 kV to 1 kV; degree of vacuum in an electron gun, P, = 0.1 Pa or less, preferably 0.01 Pa to 0.1 Pa; number of times an electron beam is applied (at about 0.2 Hz) N = 1 to 20; and distance from the lower tip of the electron gun to the base material L = 5 mm to 50 mm. The base material may have magnets attached to its bottom. When magnets are provided, an electron beam can be caused to squeeze.

4. <Decrease in Platelet Adhesion of Surface in Contact with Blood following Electron Beam Irradiation>

[0017] A titanium or titanium alloy base material subjected to electron beam irradiation in Step 3 above was held in a flow chamber, where blood modified to have a hematocrit of 40% and a platelet count of $1.5 \times 10^5/\mu L$ was refluxed to circulate at a flow rate of 6 ml/h for 10 minutes. The specimen of the titanium or titanium alloy base material recovered from the flow chamber was washed, and the platelets adherent to the surface were fixed, dehydrated, and lyophilized, whereupon the state of the platelets adherent to the surface and the shape change of platelets occurring with activation were observed with a scanning electron microscope (SEM). FIG. 4 illustrates a structure of the flow chamber used in an exploded perspective.
The flow chamber illustrated in FIG. 4 comprises a silicone plate b, the titanium or titanium alloy base material, a Teflon™ spacer c, a coating slide glass plate d, a silicone plate e, and a metallic plate f, all fitted in this order into an acrylic substrate a and fastened together with a screw g tighetend to a given torque. The Teflon™ spacer has a cut-out square central portion (measuring e.g., 10 mm x 10 mm). Blood supplied by a blood feeder such as a syringe pump through an inlet of the acrylic substrate passes through a gap between the coating slide glass plate and the titanium or titanium alloy base material, i.e., the cut-out portion of the Teflon™ spacer, and is discharged through an outlet of the acrylic substrate.

FIG. 5 illustrates platelets adherent to the specimen 1A not subjected to electron beam irradiation. FIG. 6 illustrates platelets adherent to the specimen 21A subjected to electron beam irradiation. It is apparent that the titanium or titanium alloy base material surface has a platelet adhesion that is considerably reduced by the electron beam irradiation. After the electron beam irradiation, not only does the surface have a reduced count of adherent platelets, but activation of platelets is inhibited on the surface as illustrated in Examples described later.

(Observation of Craters)

[0018] It was shown that the method in which end milling of the titanium or titanium alloy base material is followed by the electron beam irradiation proved to yield a titanium or titanium alloy base material surface that, when in contact with blood, has a reduced platelet adhesion. However, observation of the titanium or titanium alloy base material surface revealed defects called craters that were caused depending on conditions. FIG. 8 shows a crater observed with an atomic force microscope (referred to as "AFM" below). FIG. 9 is a metallographic micrograph (20x magnification) showing a surface having craters.
The craters have a depth of about 2.1 μm and is considered to have been caused by impurities inside the base material or matter that might have fallen from above the base material due to electron beam irradiation. It was also found by observation that the frequency at which craters are generated during the electron beam irradiation following the machining changes depending on machining speed, machining means, and applied load.
When the titanium or titanium alloy base material surface has small pits (so-called craters) that may be caused by electron beam irradiation, the surface, when in contact with blood as the base material is used in a medical device, is liable to retain blood or allow a blood clot to form, impairing its biocompatibility.

5. <Reduction of Craters>

[0019] It was found that when the surface is subjected to heat treatment in a process preceding the electron beam irradiation, the craters generated during the electron beam irradiation can be reduced. This is considered to be attributable to thermal expansion of crystal grains that were reduced in size by the cutting process.
Any one of the following methods may be implemented:

(1) a method of vacuum-annealing the titanium or titanium alloy base material surface after the cutting process, wherein vacuum annealing is implemented under conditions for example, that the degree of vacuum $P = 8 \times 10^{-3}$ Pa, preferably 0.001 Pa to 0.1Pa, and the holding temperature x time = 800°C x 1 hour, preferably 500°C to 900°C for 30 minutes to 3 hours, followed by slow cooling to a room temperature, the vacuum annealing being followed by the electron beam irradiation, and
(2) a plasma cathode electron beam irradiation method.

[0020] As a plasma cathode electron beam irradiator, use may be made of, for example, SOLO (electron beam generator manufactured by Nagata Seiki Co, Ltd.). FIG. 10 is a schema thereof. SOLO comprises a hollow cathode 21 and a hollow anode 25 to generate plasma, which serves as a cathode. An electron beam is allowed to pass through a DC-biased grid 29 for acceleration and, passing through a drift tube 31, irradiates a sample 33 on a holder 49. An electron beam having an irradiation area measuring 1 mm to 10 mm in diameter near the sample, which is a titanium or titanium alloy base material, scans the sample. An end-milled surface of a 6-4 alloy is scanned with a plasma cathode electron beam preferably using the SOLO system illustrated in FIG. 10 under the following conditions:

Cathode current I = 50 A to 200 A; acceleration voltage Vacc = 10 kV to 30 kV; degree of vacuum, or Ar gas pressure, in an electron gun, P, = 1×10^{-2} Pa to 10×10^{-2} Pa; number of times an electron beam is applied at about 0.5 Hz to 20 Hz, N, = 1000 to 5000; and frequency f = 0.5 Hz to 20 Hz. A cover made of titanium foil is provided above the base material. After irradiation, the sample is slowly cooled inside the irradiator. FIG. 2(B) illustrates an image acquired by a TEM showing a cross section of a base material irradiated by SOLO in Example 2. FIG. 2(A) shows size reduction of crystal grains that occurred after the cutting process; FIG. 2(B) shows enlargement of crystal grains that occurred after the irradiation by SOLO. The inventors infer that the enlargement of crystal grains reduced the crystal grain boundary and caused impurities to float from the base material, so that the occurrence of craters is inhibited during the electron beam irradiation to follow.

6. <Electron Beam Irradiation after Crater Reduction Process>

[0021] The same electron beam irradiation as in Step 3 above is applied. Step 5 above and Step 6 yield a titanium or titanium alloy base material surface having a reduced platelet adhesion when in contact with blood and an inhibited occurrence of craters.

7. <Multistage Electron Beam Irradiation>

[0022] After end milling, first electron beam irradiation is implemented with a relatively low cathode voltage, followed by second electron beam irradiation with a cathode voltage that is higher than that used in the first electron beam irradiation.
The irradiation is preferably implemented with a first cathode voltage applied, Vc = 5 kV to 20 kV. While the other conditions than the cathode voltage are not specified, it is preferable that solenoid voltage Vs = 0.1 kV to 1 kV; degree of vacuum in an electron gun, P, = 0.1 Pa or less (no lower limit is particularly specified but because a high degree of vacuum is uneconomical, a range of 0.01 Pa to 0.1 Pa may be used); number of times an electron beam (at about 0.2 Hz) is applied, N, = 1 to 20; and distance from the lower tip of the electron gun to the base material, L, = 5 mm to 50 mm.
The second electron beam irradiation is implemented with a cathode voltage that is 5 kV to 10 kV higher than that of the first electron beam irradiation.
While the other conditions than the cathode voltage are not particularly specified, the same conditions may be used as in the first electron beam irradiation.

8. <Pure titanium is used as an anode to implement electron beam irradiation in reverse polarity.>

[0023] Pure titanium is used as an anode to implement electron beam irradiation in reverse polarity. FIG. 15 is a schema of an irradiator used. The irradiator is basically the same as the electron beam irradiator illustrated in FIG. 3.
In FIG. 15, a base material (sample) is disposed at an upper cathode 70, and pure titanium is disposed at a lower anode 72. The upper cathode is the base material; the lower target is pure titanium. While irradiation conditions are not particularly specified, it is preferable that the cathode voltage is relatively high with Vc = 20 kV to 30 kV, and the number of irradiation N = 10 to 60 at 0.1 Hz to 1 Hz.
In the process, the inventors observed not only that the titanium from the lower anode was deposited by sputtering on the cathode base material surface but that impurities were ejected explosively from near the surface of the upper cathode base material, creating cathode spots.
Thereafter, the multistage electron beam irradiation described in Step 7 above is preferably applied. The one-stage electron beam irradiation described in Step 2 above may instead be applied.

9. <Surface Coating Method>

[0024] The titanium or titanium alloy base material surface obtained in any of Steps 3 to 8 above may be further coated with a thin film composed of a substance different from the titanium or titanium alloy base material. The substance for coating the surface is exemplified by organic substances such as diamond-like carbon (DLC) deposited by chemical vapor deposition (CVD), DLC deposited by physical vapor deposition (PVD), and PTFE.
Coating a surface-treated titanium or titanium alloy base material with a thin film composed of a substance different from the titanium or titanium alloy base material produces additonal effects of lowering the static friction coefficient of the surface, preventing scratches from occurring, and enhancing antithrombogenicity. Evaluation was made to determine whether, when the base material surface is coated with a thin film composed of a substance different from the base material, the above electron beam irradiation poses any problem to the thin film deposition process. As described in detail below in Example 6 with reference to an example of a diamond-like carbon (DLC) coat deposited by PVD, adhesion between the film deposited as an upper layer and the electron beam-irradiated titanium or titanium alloy base material was examined. The results obtained in Example 6 show that the electron beam irradiation of the invention does not pose any problem to the deposition of the thin film as an upper layer.

10. <Medical Device>

[0025] The kind and the structure of the medical device obtained by the manufacturing method of the invention are not specifically limited. The medical device of the invention comprises a machined metallic surface that comes into contact with blood, body fluid, or tissue. The medical device of the invention is exemplified by a pump in an artificial heart lung system; a blood pump; a cardiac pacemaker; a denture, an artificial bone, a bolt for implant, and other implants; a guide wire; and a stent. Examples include, more specifically, a stent and a blood pump made using a titanium material or a titanium alloy.
Shown in FIGS. 20 to 22 is another example, "a blood pump device 100 comprising: a housing 120 including a blood inlet port 122 and a blood outlet port 123; a pump section 200 including an impeller 121 provided with magnetic members 125 and adapted to turn inside the housing 120 to feed blood; and an impeller turning torque generator 300 adapted to

suck and turn the impeller 121 of the pump section 200, wherein the pump section 200 further includes dynamic pressure grooves 138 provided in the housing's inner surface on the impeller turning torque generator 300 side or in the surface of the impeller which is on the impeller turning torque generator 300 side, and wherein the impeller 121 turns out of contact with the housing 120." Such blood pump devices are described in detail in JP 2005-270345 A and JP 2005-287598 A.

[0026] The blood pump of the invention is not specifically limited, and the centrifugal blood pump device 100 illustrated in FIGS. 20 to 22 may be explained by way of example, in which the impeller 121 having magnetic members embedded therein is turned by the rotation of a rotor 131 having magnets 133 of the impeller turning torque generator 300 and is turned without contacting the inner surface of the housing 120 owing to a pressure generated by the dynamic pressure grooves 138 during rotation, as illustrated in FIGS. 20 to 22.

The housing 120 is made of non-magnetic substance such as a titanium or titanium alloy base material and comprises a blood chamber 124. The housing 120 accommodates the impeller 121. As illustrated in FIG. 21, the blood outlet port 123 is provided so as to project in a tangential direction from a lateral portion of the housing 120 having a substantially cylindrical shape.

As illustrated in FIG. 20, the blood chamber 124 provided in the housing 120 accommodates the impeller 121 having the shape of a disk with a centrally located through-hole. The impeller 121 comprises an annular plate member 127 (lower shroud) forming a lower surface, an annular plate member 128 (upper shroud) forming an upper surface and having a centrally located opening, and a plurality of vanes 118 provided between the plate members 127 and 128. Between the lower shroud and the upper shroud, there are formed a plurality of blood passages 126 divided by adjacent vanes 118. The blood passages 126 communicate with the central opening of the impeller 121 and extend from the central opening of the impeller 121 to the outer periphery, each with a gradually increasing width, as illustrated in FIG. 21.

[0027] The impeller turning torque generator 300 of the blood pump 100 in this example is totally free from contact with blood. By contrast, the inner surfaces of the housing section on the blood inlet port side and the housing section on the torque generator side, the dynamic pressure grooves provided in one or both of the housing sections, and, where necessary, the impeller, as well as other components where necessary, are provided with, for example, a cover made of a titanium or titanium alloy base material, these components having surfaces that come into contact with blood. Where these components have a titanium or titanium alloy base material surface subjected to at least cutting process, and when manufactured by the method of the invention, the platelet adhesion of the surfaces that come into contact with blood can be reduced, and their utility can be enhanced.

Further, another manufacturing method of the invention enables production of a highly biocompatible blood pump device that reduces the platelet adhesion of a surface coming into contact with blood and inhibits the formation of craters, reducing the defects of permitting collection of blood or easy formation of blood clots on the surface in contact with blood.

EXAMPLES

[0028] The present invention is described in detail below with reference to Examples, which by no means limits the scope of the present invention to the Examples.

(Example 1)

1. End Milling

[0029] The surface roughness of an end-milled surface of an ELI base material (manufactured by Allegheny Ludlum NJ USA, Grade 23) (specimen No. 1A) was observed with a metallograph and a laser microscope; the photographs obtained are shown respectively in FIG. 1(A) (20x magnification) and FIG. 1(B). In both photographs, traces of machining were observed clearly.

The end milling was implemented using MTV515/40N, a high-speed machining center manufactured by YAMAZAKI MAZAK CORPORATION at a turning speed of 750 rpm and a feed rate of 30 mm/min. for 30 minutes.

The surface roughness, shown in FIG. 1C, was measured using Nanopikos 1000 manufactured by Seiko Instruments Inc. A span of 149 μm was also among the measuring conditions.

FIG. 2(A) shows a photograph of an image acquired by a TEM (transmission electron microscope) representing a cross section of an end-milled base material. It was observed how crystal grains before the machining decreased in size through the cutting process.

2. Electron Beam Irradiation

[0030] Apart from the above, a 6-4 alloy was end-milled under the same conditions as in Step 1 above to obtain the specimen No. 21A, which underwent electron beam irradiation by a large-area electron beam irradiator illustrated in

FIG. 3 under the following conditions: applied cathode voltage Vc = 17 kV, solenoid voltage Vs = 0.5 kV, degree of vacuum in an electron gun P = 0.05 Pa, number of times an electron beam is applied (at about 0.2 Hz), N, = 7, and distance from the lower tip of the electron gun to the base material, L, = 20 mm. The surface roughnesses of the specimen No. 1A, an ELI material that was end-milled but not subjected to electron beam irradiation, and the 6-4 alloy, which was end-milled and subjected to electron beam irradiation using the large-area electron beam irradiator illustrated in FIG. 3, were measured. The obtained surface roughnesses were compared as shown in Table 1.
An ELI material was used as the specimen No. 1A (hereinafter referred to as specimen 1A) and a 6-4 alloy was used as the specimen No. 21A (hereinafter referred to as specimen 21A) in order to show that, in examples where electron beam irradiation of the invention is implemented, similar results are obtained regardless of whether one may use a 6-4 alloy having a lower purity or an ELI material, the specimen 1A being used as a comparative material for showing that traces of end-milling are left.

[0031] The obtained measurements of surface roughness are as follows. The same measuring conditions were used as in the measuring implemented after machining described in Step 1 above.

[Table 1]

Specimen No.	Measuring distance (μm)	Ra(μm)	Ry(μm)	Rz(μm)
1A	149	0.539	2.640	2.008
21A	149	0.083	0.370	0.266

3. Platelet Adhesion Test

(1) Observation of Adherent Platelets

[0032] The obtained specimens 1A and 21A were each held beneath the Teflon™ spacer in the flow chamber illustrated in FIG. 4, and blood modified to have a hematocrit value of 40% and a platelet count of $1.5 \times 10^5/\mu l$ was refluxed to circulate at a flow rate of 6.0 ml/h for 10 minutes. The specimens were recovered from the flow chambers, whereupon washing, fixing the platelet, dehydration, and lyophilization were carried out. FIGS. 5 and 6 show photographs representing the adherent platelets of the specimen surfaces as observed with a scanning electron microscope (SEM).
FIG. 5(A) shows the adherent platelets to the specimen 1A. FIG. 5(B) shows a metallic surface that is out of contact with blood flow for comparison.
FIG. 6(A) shows the adherent platelets to the specimen 21A. FIG. 6(B) shows a metallic surface that is out of contact with blood flow for comparison.
It is apparent that the specimen 21A subjected to the electron beam irradiation shows a smaller number of platelets adherent to the surface in comparison with the end-milled specimen 1A.

(2) Evaluation of Platelet Shape Change associated with Activation

[0033] Platelet shape change associated with the activation thereof was observed from the results obtained in FIGS. 5 and 6. FIG. 7 schematically illustrates shape change of a platelet associated with its activation, where the shape change is broken down into five forms defined as follows: R: Round; D: Dendritic; SD: Spread Dendritic; S: Spreading; and FS: Fully Spread. The definition is made according to the classification described by Steven L. Goodman in FIG. 11 of J. Biomed Mater Res, 45, 240-250 (1999). Note that "A" is used in the above literature in lieu of "R".

[0034]

[Table 2]

Test piece No.	R	D	SD	S	FS	Total
1A	0	22	23	23	15	83
21A	1	13	8	6	6	34

Table 2 shows the numbers of the respective forms of platelets resulting from shape change occurring in association with activation in a field of view of $1.25 \times 10^4\ \mu m^2$.
It is apparent from the results shown by Table 2 that the titanium or titanium alloy base material surfaces subjected to the electron beam irradiation after the machining not only had smaller numbers of platelets adherent thereto, but platelet

shape change occurred less, indicating that the activation of platelets was inhibited.

(Example 2)

[0035] The surface of a 6-4 alloy that was end-milled as in Example 1 was scanned with a plasma cathode electron beam using the SOLO system illustrated in FIG. 10 under the following conditions:

Cathode current I = 100 A; acceleration voltage Vacc = 15 kV; degree of vacuum and Ar gas pressure in an electron gun, P, = 3.5 x 10^{-2} Pa; number of times an electron beam (having an irradiation area measuring about 5 mm in diameter near the base material) is applied at a frequency of about 20 Hz, N, = 5,000. A cover made of titanium foil was provided above the base material. After irradiation by SOLO, the sample was slowly cooled inside the irradiator.

FIG. 2(B) illustrates an image acquired by a TEM and showing a cross section of a SOLO-irradiated base material. On the 6-4 alloy surface end-milled in Example 1 (comparative material), crystal grains decreased in size after the cutting process as observed in FIG. 2(A) whereas enlargement of crystal grains occurred after SOLO irradiation as observed in FIG. 2(B). The plasma cathode electron beam irradiation was implemented, followed by electron beam irradiation using the irradiator illustrated in FIG. 3 under the following conditions:

Vc = 20 kV, Vs = 0.5 kV, P = 0.05 Pa, N = 15, and L = 20 mm. In addition, magnets were provided at the bottom of the base material.

FIG. 11(A) shows the resultant surface of the base material observed with a surface laser microscope. FIG. 12 shows an image of the base surface acquired in a broad range by a metallograph (20x magnification).
FIG. 11(B) shows measurements of surface roughness. Measurements of surface roughness obtained include:

Ra: 0.055 μm, Ry: 0.290 μm, and Rz: 0.262 μm, over a distance of 149.00 μm.

(Example 3)

[0036] After end-milling, plasma cathode electron beam irradiation was implemented with SOLO as in Example 2 above except that an ELI material was used as titanium or titanium alloy base material, followed by the same electron beam irradiation as implemented in Example 2. FIG. 13 shows a photograph representing the result as acquired by a surface microscope.

(Example 4)

[0037] A 6-4 alloy was end-milled under the conditions used in Example 1 and thereafter subjected to the first electron beam irradiation with a relatively low voltage of 17 kV. Electron beam irradiation was effected under conditions as follows: applied cathode voltage Vc = 17 kV, solenoid voltage Vs = 0.5 kV, degree of vacuum in an electron gun, P, = 0.05 Pa, number of times an electron beam is applied (at about 0.2 Hz), N, = 10, and distance from the lower tip of the electron gun to the base material L = 20 mm.
Subsequently, the second electron beam irradiation was implemented with 25 kV, a voltage that is higher than that used in the first electron beam irradiation. Electron beam irradiation was effected under conditions as follows: applied cathode voltage Vc = 25 kV, solenoid voltage Vs = 0.5 kV, degree of vacuum in an electron gun, P, = 0.05 Pa, number of times an electron beam is applied (at about 0.2 Hz), N, = 10, and distance from the lower tip of the electron gun to the base material L = 20 mm.
FIG. 14(A) shows a surface micrograph (20x magnification) acquired by a metallograph and representing a base material surface after the first electron beam irradiation; FIG. 14(B) shows a surface micrograph (20x magnification) acquired by a metallograph and representing the base material surface after the second electron beam irradiation following the first electron beam irradiation. In FIG. 14(A), a number of craters and traces of machining were detected. In FIG. 14(B), traces of machining were not seen, and the number of craters decreased.

(Example 5)

[0038] The irradiator illustrated in FIG. 15 was used. A sample, the specimen 1A obtained by end-milling an ELI material in Example 1, was disposed at the upper cathode 70, and pure titanium was disposed at the lower anode 72. Electron beam irradiation was implemented with a cathode voltage of Vc = 28 kV, N = 40 times over.
In the process of melt and cooling during the first electron beam irradiation, MnS or MC-based carbide for example, are

produced immediately beneath craters. Reverse-polarity electron beam irradiation is considered to produce effects of blowing away the above products as an electron beam is applied.
In the process using reverse polarity, the inventors observed not only that the titanium arriving from the lower anode was deposited by sputtering on the cathode product but that impurities were ejected explosively from near the surface of the upper cathode product, creating cathode spots.
Subsequently, two-stage electron beam irradiation was implemented under the same conditions as in Example 4. FIG. 16 shows a surface micrograph (20x magnification) of the resultant base material surface acquired by a metallograph. The result shown in FIG. 16 revealed no craters. The entire irradiation implemented consisted of [reverse-polarity irradiation (28 kV) - straight polarity irradiation (17 kV) - straight polarity irradiation (25 kV)].

(Example 6)

[0039] The surfaces of the titanium or titanium alloy base materials obtained in Examples 3 to 5 were coated with diamond-like carbon (DLC).
The coating was implemented by GPAS (Graphite Pulse Arc Sputtering) method (US Patent No. 6,753,042). The DLC films on equivalent specimens had a thickness in a range of 1.0 μm to 1.2 μm.
A Rockwell indenter was press-inserted to examine the adhesion of the DLC film, the surface coating material, and a high-speed reciprocating motion was caused with a load applied to the indenter to evaluate the abrasion in order to examine the abrasion resistance. The Rockwell indenter was press-inserted with 150 kg, and the abrasion was evaluated by causing a reciprocating motion using a HEIDON Type 14DRa, a tribo-tester manufactured by Shinto Scientific Co., Ltd., with a load of 100 g, at a speed of 1,200 mm/min, and with a stroke of 6 mm, 2000 times over.
Results are shown in FIGS. 17 to 19. FIGS. 17(A), 18(A), and 19(A) show the resultant Rockwell indentations; FIGS. 17(B), 18(B), and 19(B) show the results of abrasion resistance evaluation.
In the case shown in FIG. 17 illustrating a surface obtained in Example 3 and coated with DLC, some detachments were observed near the Rockwell indentation but the adhesion posed no practical problems.
In the case shown in FIG. 18 illustrating a surface obtained in Example 4 and coated with DLC, adhesion was judged to pose no practical problems.
In the case shown in FIG. 19 illustrating a surface obtained in Example 5 and coated with DLC, adhesion was excellent.

(Comparative Example 1)

[0040] Pure titanium was deposited by magnetron sputtering on the surface of the specimen 1A obtained in Example 1. In this case, the sputtered film detached in the subsequent electron beam irradiation process, and the surface thus obtained was of no practical use.

REFERENCE SIGNS LIST

[0041]

1 vacuum chamber, 2 vacuum pump, 3 auxiliary vacuum pump, 4 argon gas container, 5 solenoid, 6 anode, 7 cathode, 8 anode plasma,
9 cathode sample a acrylic substrate, b silicone plate, c Teflon™ spacer, d HEMA/St block copolymer coating slide glass plate, e silicone plate, f metallic plate, g screw
20 SOLO system, 21 hollow cathode, 25 hollow anode, 29 grid, 31 drift tube, 33 sample, 49 holder
70 upper cathode (sample), 72 lower anode (pure titanium) 100 centrifugal blood pump device, 200 centrifugal blood pump section
300 impeller turning torque generator, 118 vane
120 housing, 121 impeller
122 blood inlet port, 123 blood outlet port 124 blood chamber, 125 embedded magnetic member (permanent magnet)
126 blood passage, 127 annular plate member (lower shroud) 128 annular plate member (upper shroud), 131 rotor
133 permanent magnet, 134 motor, 138 dynamic pressure groove

Claims

1. A method of manufacturing a medical device comprising subjecting a titanium or titanium alloy base material surface having undergone at least a cutting process to electron beam irradiation to reduce platelet adhesion of a surface that comes into contact with blood.

2. The method of manufacturing a medical device according to Claim 1, wherein the electron beam irradiation is implemented after the surface is heat-treated.

3. The method of manufacturing a medical device according to Claim 1 or 2, wherein the electron beam irradiation comprises a first electron beam irradiation implemented with a first voltage and a second electron beam irradiation implemented with a second voltage that is higher than the first voltage.

4. The method of manufacturing a medical device according to any one of Claims 1 to 3, wherein the electron beam irradiation is implemented by reverse-polarity electron beam irradiation using a pure titanium metal as an anode, followed by straight-polarity electron beam irradiation.

5. The method of manufacturing a medical device according to Claim 4, wherein the straight-polarity electron beam irradiation is implemented at least twice under different conditions.

6. The method of manufacturing a medical device according to any one of Claims 1 to 5, wherein the surface subjected to the electron beam irradiation is coated with a thin film composed of a substance that is different from the base material.

7. The method of manufacturing a medical device according to Claim 6, wherein the substance that is different from the base material is diamond-like carbon.

8. The method of manufacturing a medical device according to any one of Claims 1 to 7, wherein the medical device is a blood pump device.

9. The method of manufacturing a medical device according to Claim 8, wherein the blood pump device is a centrifugal blood pump device including dynamic pressure grooves.

10. A blood pump device obtainable by the method of manufacturing a medical device according to Claim 8 or 9.

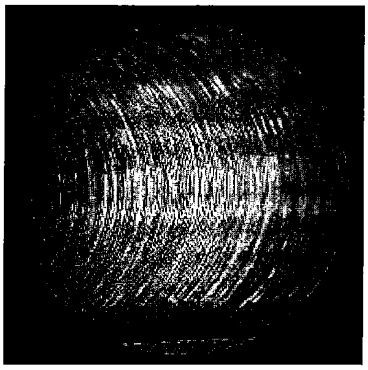


FIG. 1(A)

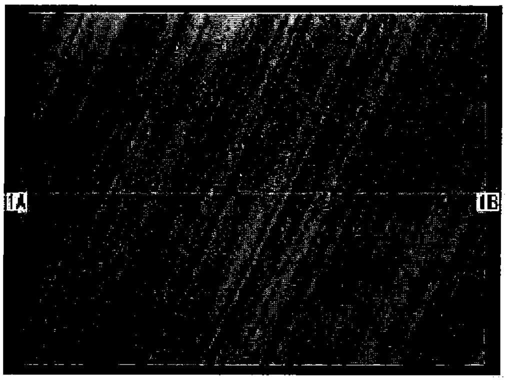


FIG. 1(B)

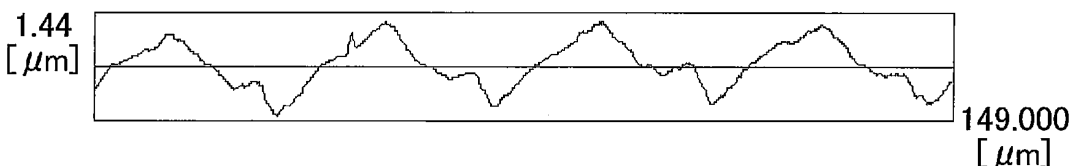


FIG. 1(C)

FIG. 2(A)

FIG. 2(B)

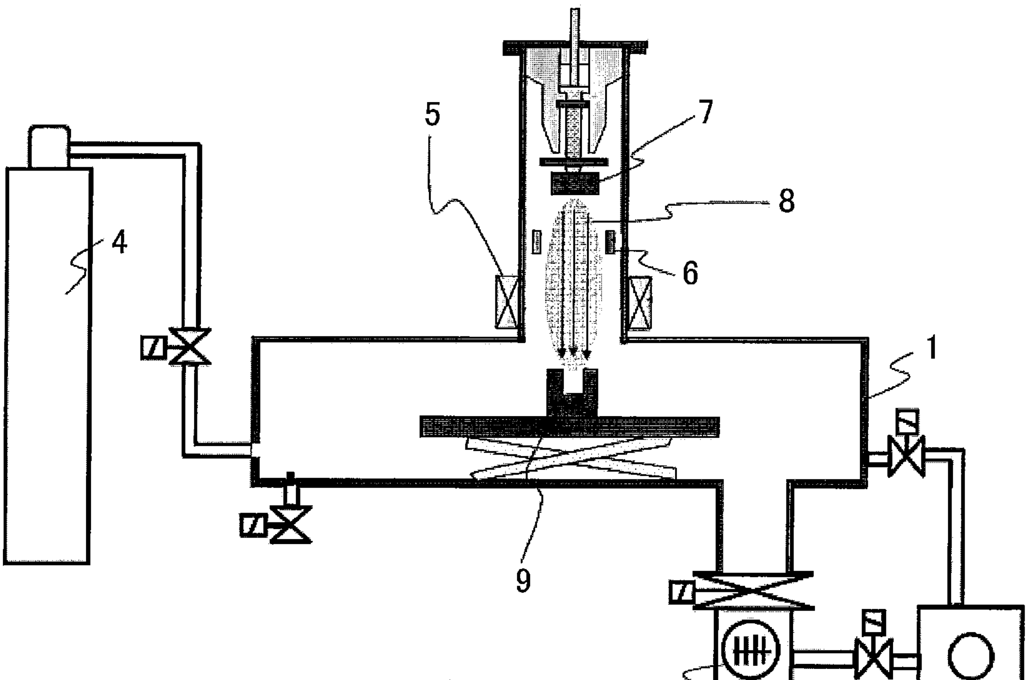


FIG. 3

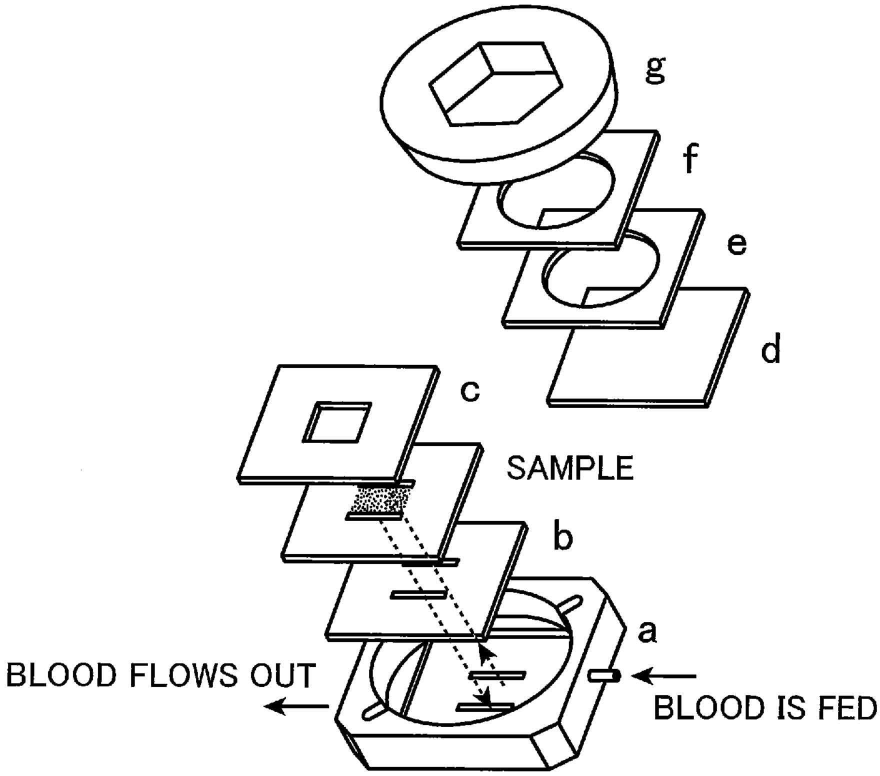

g
f
e
d
c
SAMPLE
b
a
BLOOD FLOWS OUT
BLOOD IS FED

FIG. 4(A)

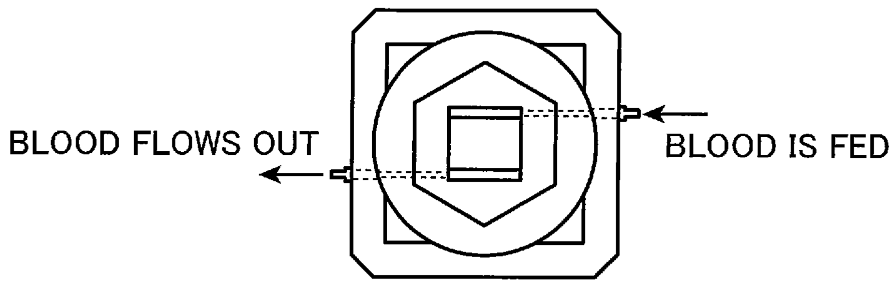

BLOOD FLOWS OUT
BLOOD IS FED

FIG. 4(B)

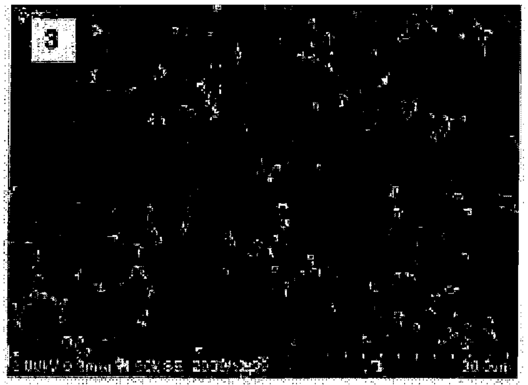


FIG. 5(A)

FIG. 5(B)

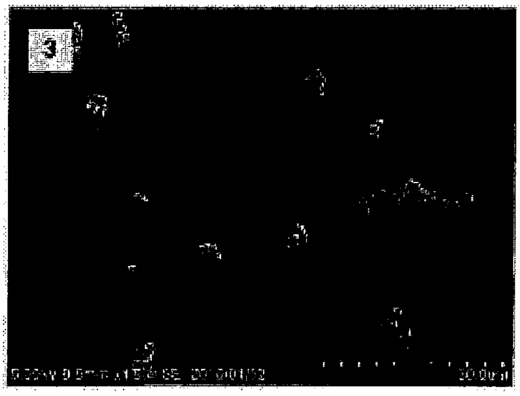


FIG. 6(A)

FIG. 6(B)

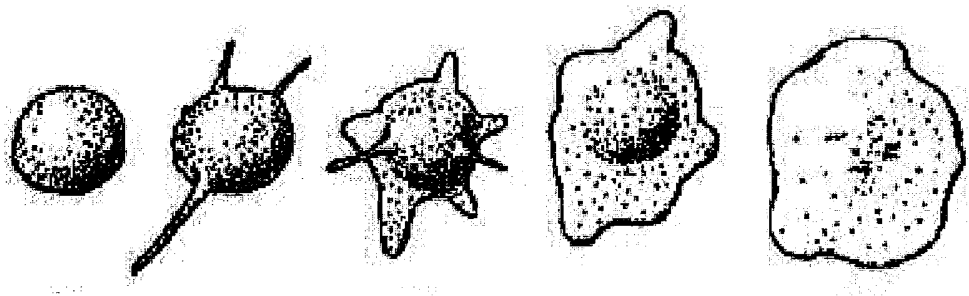


FIG. 7

FIG. 8

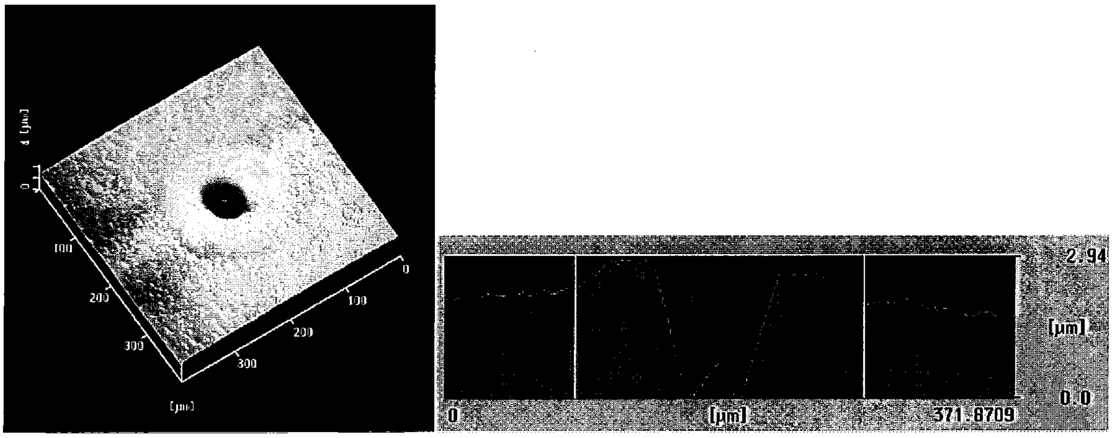


FIG. 9

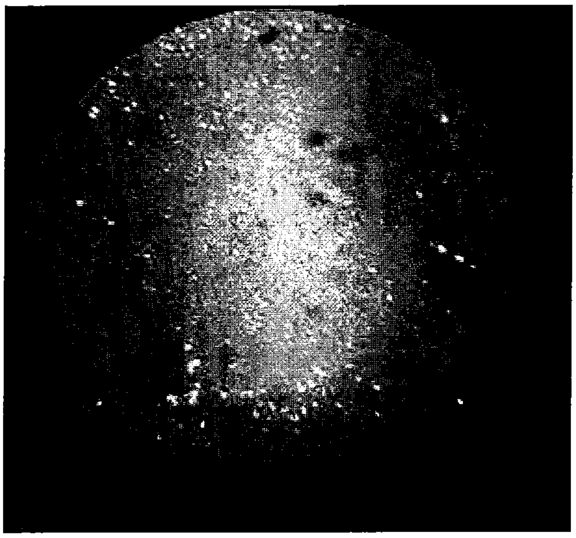
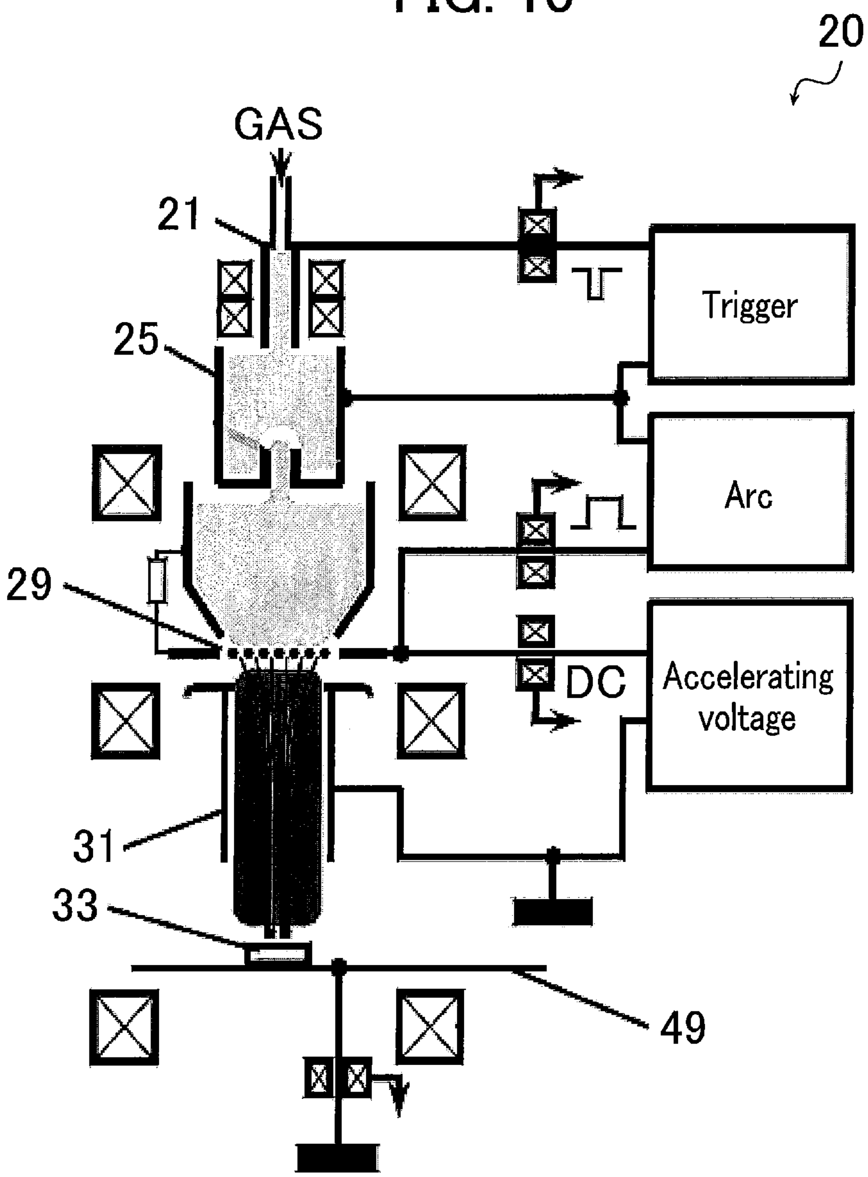


FIG. 10



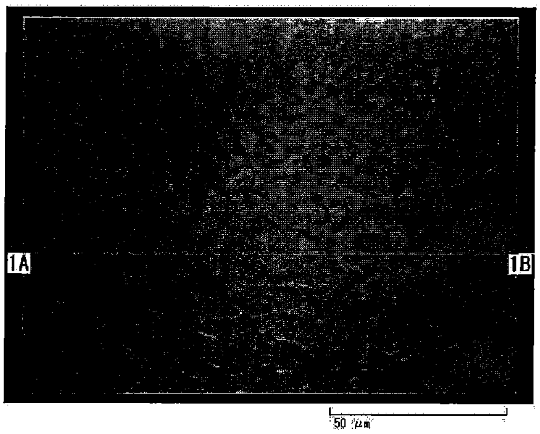


FIG. 11(A)

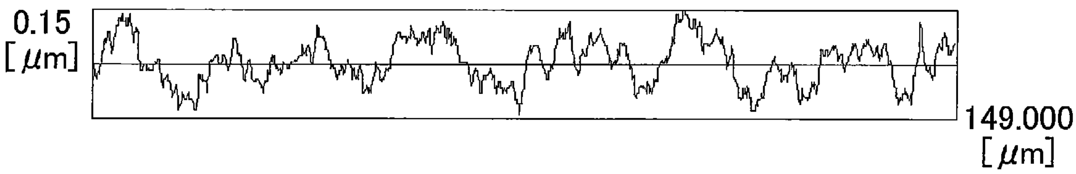


FIG. 11(B)

FIG. 12

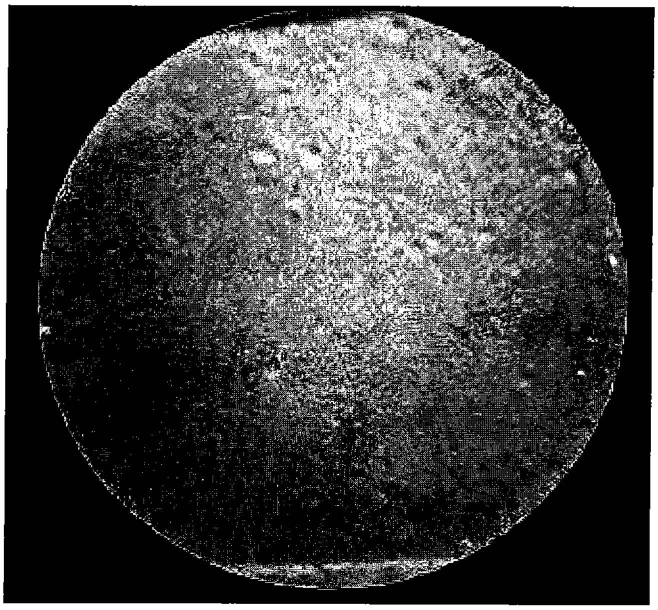
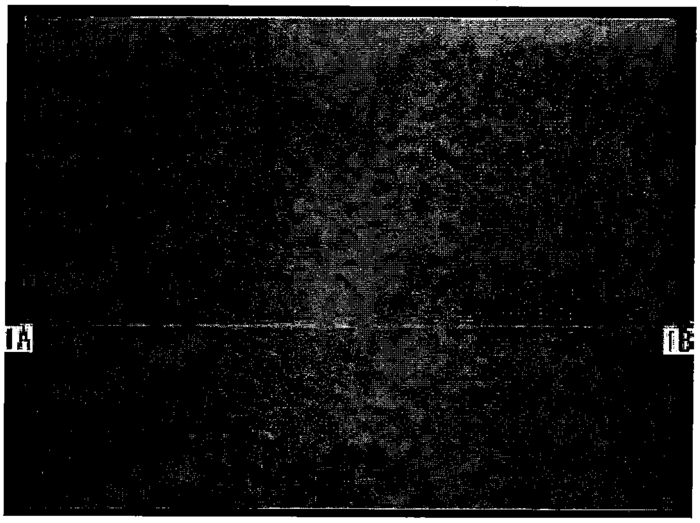


FIG. 13



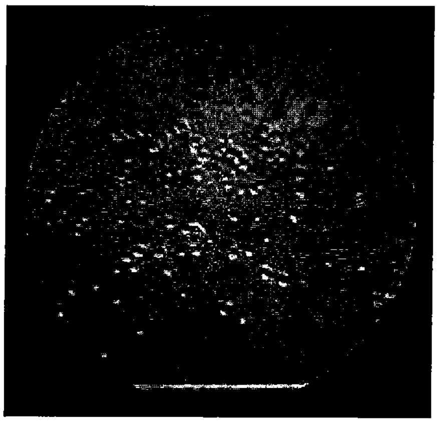


FIG. 14(A)

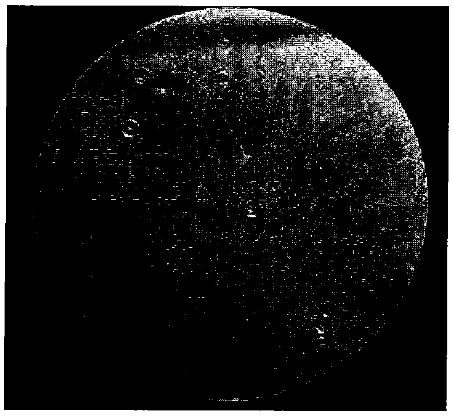


FIG. 14(B)

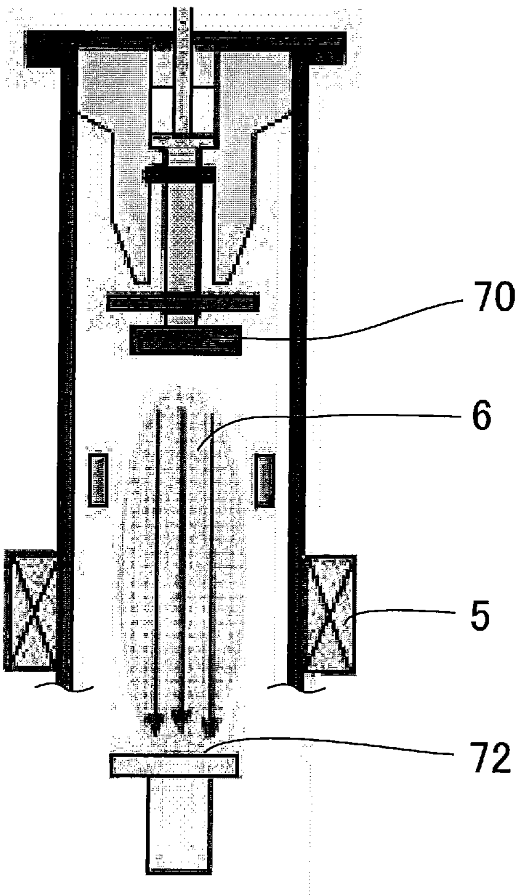
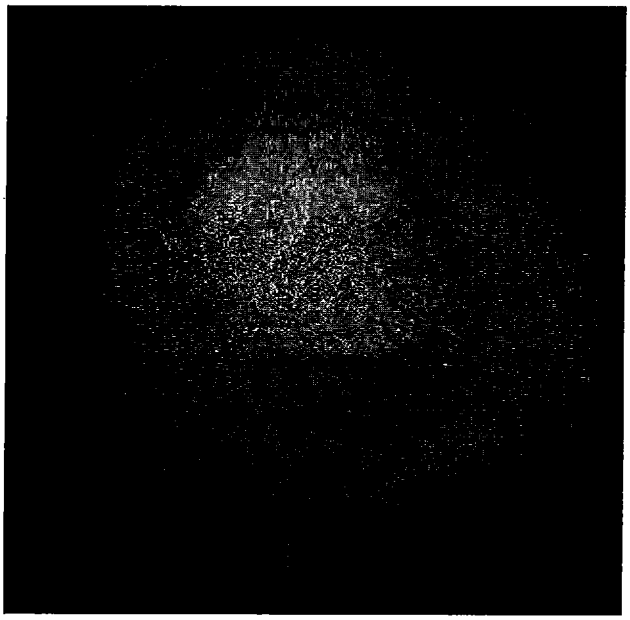
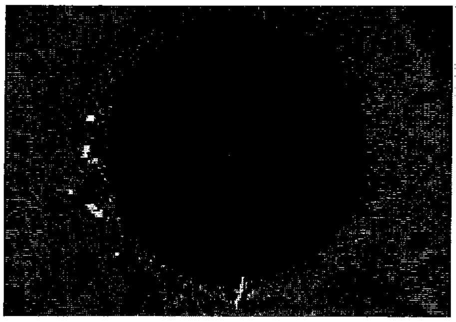


FIG. 15

FIG. 16





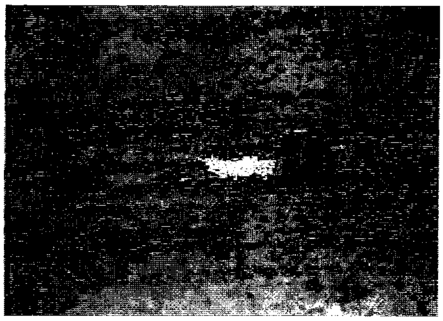


FIG. 17(A) FIG. 17(B)

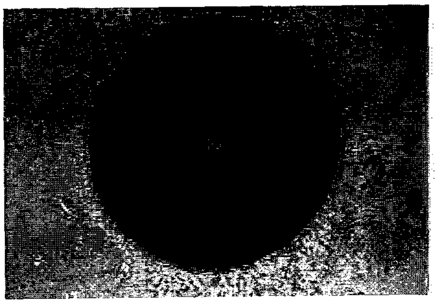


FIG. 18(A)

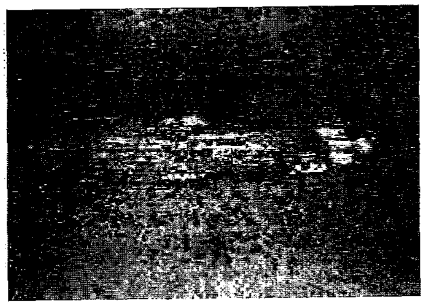


FIG. 18(B)

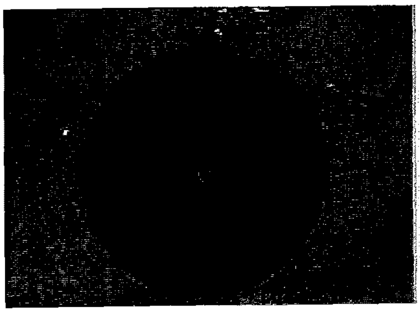


FIG. 19(A)

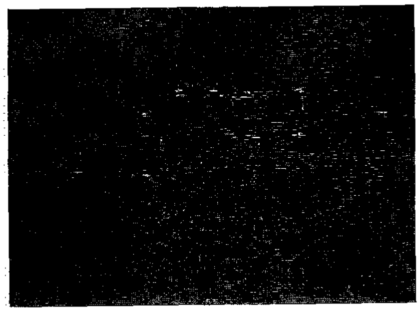


FIG. 19(B)

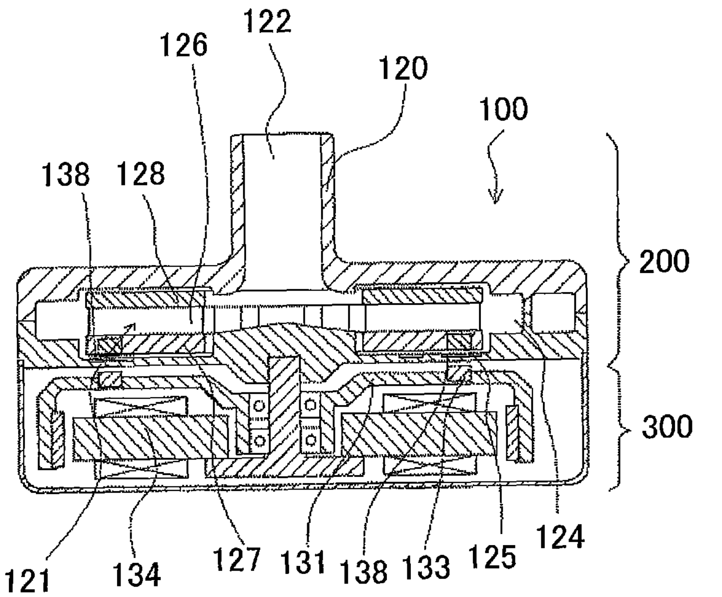


FIG. 20

FIG. 21

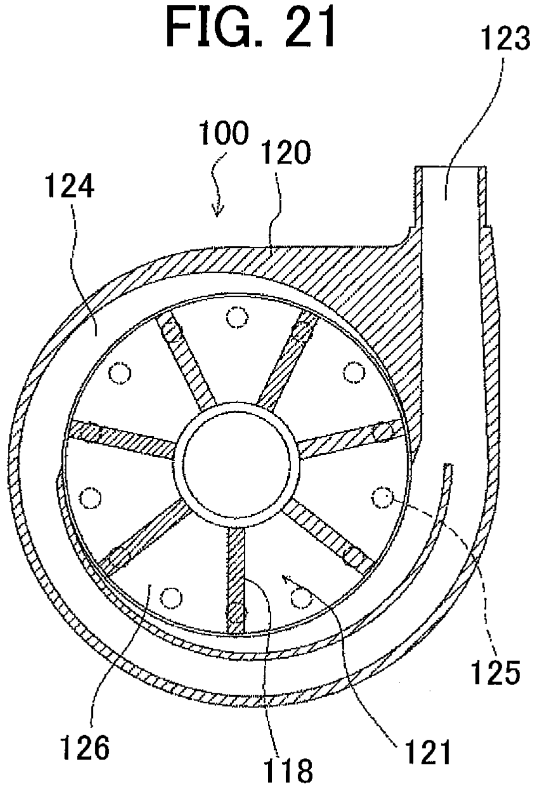
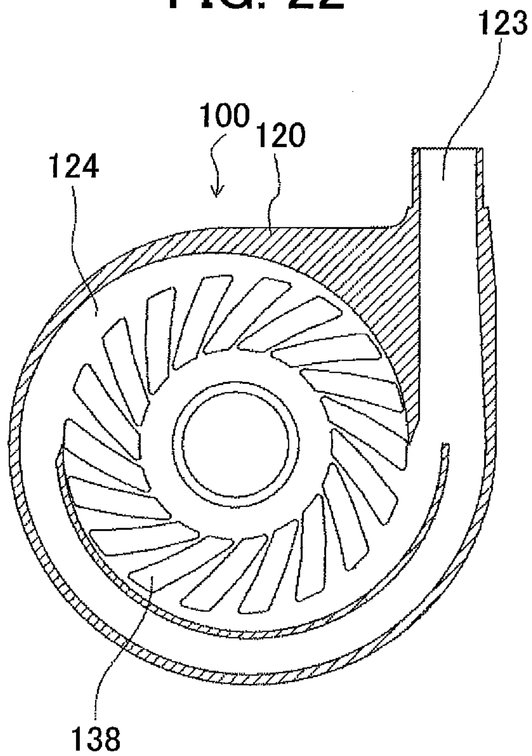


FIG. 22



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/071110

A. CLASSIFICATION OF SUBJECT MATTER
A61L31/00(2006.01)i, *A61M1/10*(2006.01)i, *A61N1/362*(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L31/00, A61M1/10, A61N1/362

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho	1922-1996	Jitsuyo Shinan Toroku Koho	1996-2011
Kokai Jitsuyo Shinan Koho	1971-2011	Toroku Jitsuyo Shinan Koho	1994-2011

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA/MEDLINE/EMBASE/BIOSIS(STN), JSTPlus/JMEDPlus/JST7580(JDreamII)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X Y	JP 10-248923 A (Sun Medical Technology Research Corp.), 22 September 1998 (22.09.1998), entire text; particularly, paragraphs [0015], [0031], [0032] (Family: none)	10 6-9

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 November, 2011 (08.11.11)	15 November, 2011 (15.11.11)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/071110

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	Yoshiyuki UNO et al., "High Efficiency Finishing of Biomaterial Titanium Alloy by Wide-area Electron Beam Irradiation", The Japan Society of Mechanical Engineers Manufacturing & Machine Tool Division Koenkai Koen Ronbunshu, 2004, vol.5th, pages 279 to 280, ISSN: 1348-3943	6-10
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Y	Junko TOKUNAGA et al., "Surface modification of dental alloy by electron-beam system (Part 4) : Examination on the surface of Titanium and Au-Ag-Pd alloy", The Journal of the Japanese Society for Dental Materials and Devices, 2005, vol.24, no.5, page 407, ISSN: 0286-5858	6-10
Y	Tokunaga J. et al., Large-area electron beam irradiation for surface polishing of cast titanium., Dental Materials Journal, 2009, Vol.28, No.5, pages 571 to 577, ISSN: 0287-4547	6-10
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/071110

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	JP 2005-287598 A (Terumo Corp.), 20 October 2005 (20.10.2005), fig. 5, 6 & EP 1598087 A2 & US 2005/0287022 A1	8-10

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REFERENCES CITED IN THE DESCRIPTION

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- JP 2005270345 A **[0012] [0025]**
- JP 2005287598 A **[0025]**
- US 6753042 B **[0039]**

Non-patent literature cited in the description

- **STEVEN L.** *J. Biomed Mater Res,* 1999, vol. 45, 240-250 **[0033]**